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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,949	OMARY ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-8* is/are pending in the application.

4a) Of the above claim(s) *5 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the reply of December 1, 2008. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to place all claims in condition for allowance.

All rejections not reiterated herein are hereby withdrawn. In particular, the previous objection to the specification has been withdrawn in view of the amendments to the specification. The rejection of claims 1 and 2 under 35 USC 112, first paragraph (written description) has been obviated by the cancellation of claim 2 and the amendment to claim 1. Additionally, the rejections of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Ku et al (Nov 2001), Ku et al (May 2001) and Ku et al (March 2002) have been obviated by the cancellation of claim 2 and the amendment to claim 1. Note that claim 1 has been examined only to the extent that the claim reads on the elected invention of detecting a predisposition to liver disease by assaying for a nucleic acid mutation resulting in the K8 R340H alteration. The cited Ku et al references (Nov 2001, May 2001 and March 2002) do not teach the mutation resulting in a R340H alteration in keratin K8.

This action is made final.

2. Claims 1, 3 and 5-8 are pending.

Claims 1, 3, 6 and 7 encompass the elected invention and have been examined herein.

Claims 5 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 29, 2008.

Claims 1 and 3 have been examined herein to the extent that the claims read on the elected methods which detect a genotype of K8 by assaying nucleic acids. Further, claim 1 has been examined only to the extent that the claim reads on the elected K8 R340X mutation.

Claim Objections

3. Claims 1 and 3 are objected to because the claim includes subject matter of the non-elected inventions, namely the detection of a mutation in a protein (Groups III and IV), and with respect to claims 1, the detection of the mutations other than K8 R340X.

Sequence Listing

4. The sequence listing filed on December 1, 2008 is compliant and has been entered.

Maintained Rejections

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 3, 6 and 7 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final process step of the claims. The claims are drawn to methods for detecting a predisposition to liver disease. However,

the claims recite a final step of analyzing an individual for a quantitative or qualitative change in a genotype of Keratin K8. The claims as amended also recite a wherein clause which states that it is a property of the change that it is associated with a predisposition to noncryptogenic liver disease (claim 1) or that it is a property of the mutation that it is associated with a predisposition to a noncryptogenic liver disease. However, the claims omit the essential step of actually detecting a predisposition to a liver disease or a predisposition to a noncryptogenic liver disease. The claims do not set forth how analysis of an individual for a quantitative or qualitative change in a genotype results in the detection of a predisposition to a liver disease. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for determining a predisposition to liver disease or methods for detecting a quantitative or qualitative change in a genotype of keratin K8. Further, it is noted that the preamble of claim 1 is broadly drawn to detecting a predisposition to liver disease, while the claim recites that it is a property of the change that it is associated with noncryptogenic liver disease. Since the genus of liver diseases is not limited to only noncryptogenic liver diseases, it is unclear as to what is intended to be the scope of the claims – e.g., methods which determine if an individual has a predisposition to any liver disease or methods which determine if an individual has a predisposition to noncryptogenic liver diseases.

Response to Remarks:

In the response, Applicants state that the rejection has been overcome by the amendment to the claims.

This argument and the amendment to the claims have been fully considered but are not persuasive. The amendment to the claims indicates only that it is a property of the change or the mutation that it is associated with noncryptogenic liver disease. The claims have not been amended to recite an active process step of detecting a predisposition to noncryptogenic liver disease in an individual. Accordingly, the claims remain indefinite because the omit the essential process step of detecting a predisposition to noncryptogenic liver disease in an individual.

B. Claims 6 and 7 are indefinite over the recitation of "said analyzing the genomic or mRNA sequences" because this phrase lacks proper antecedent basis since the claims do not previously recite a step of analyzing genomic or mRNA sequences.

Response to Remarks:

In the response, Applicants did not specifically address this rejection. The rejection is maintained for the reasons stated above.

New Grounds of Rejection Necessitated By Applicant's Amendments to the Claims

C. Claims 1, 3, 6 and 7 are indefinite because the claims recite a method for determining a predisposition to liver disease or noncryptogenic liver disease in an "individual human." However, the claims recite a method step of analyzing "an individual." An individual is considered to encompass both human and non-human individuals. Accordingly, the scope of the claims is unclear because the preamble of the claims is of a narrower scope than the method steps of the claims and thereby it is unclear as to whether the claims are intended to be limited to methods which analyze

and detect a predisposition to noncryptogenic liver disease in only a human individual or in any individual.

D. Claim 1 is indefinite over the recitation of "said alteration" because this phrase lacks proper antecedent basis.

E. Claims 3, 6 and 7 are indefinite over the recitation of "a mutation at position 340 of keratin K8 from CGT-> CAT." The position of 340 in keratin is in reference to the keratin protein, however CGT -> CAT refers to a nucleotide sequence. Thereby, it is unclear as to what is intended to be meant by the CGT->CAT mutation occurring at position 340 of the keratin protein.

F. Claims 3, 6 and 7 are indefinite because the claims refer to a step of analyzing for a change in genotype, but then recite that a mutation at position 340 is associated with predisposition to noncryptogenic liver disease. The claims do not set forth the relationship between the genotype and the mutation and thereby it is unclear as to how the step of analyzing for a change in a genotype is intended to result in a method wherein a mutation at position 340 is associated with a predisposition to noncryptogenic liver disease. Further, the claims recite analyzing for a change in a genotype, but do not state what the change is relative to. Thereby, it is unclear as to what would constitute a change in genotype at position 340.

Claim Rejections - 35 USC § 112 – Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a human subject at increased risk for viral hepatitis or acute fulminant hepatitis (AFH) comprising: (a) providing a nucleic acid sample from said human subject wherein the nucleic acid sample comprises a nucleic acid encoding keratin 8; (b) analyzing the sequence of the nucleic acid encoding keratin 8 to determine the identity of the nucleotides encoding codon 340; and (c) determining that said human subject has an increased risk for viral hepatitis or AFH if said human subject has the sequence CAT at codon 340 of the nucleic acid encoding keratin 8 as compared to a human subject that has the sequence CGT at codon 340 of the nucleic acid encoding keratin 8, does not reasonably provide enablement for methods for determining a predisposition to any cryptogenic or noncryptogenic liver disease in any human or nonhuman subject by determining a mutation in the keratin K8 gene resulting in a R340H substitution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was previously presented in the Office action of July 31, 2008 and has been modified herein to address the amendments to the claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1 is drawn to methods for detecting a predisposition to any type of liver disease comprising analyzing an individual for a change in a genotype, wherein "said alteration" includes a K8R340H mutation, and wherein the change in the genotype is associated with a predisposition to a noncryptogenic liver disease. Claim 1 does not clarify the relationship between the alteration at K8 R340H and the change in genotype and thereby does not specify what change in genotype is associated with a predisposition to a noncryptogenic liver disease.

Claims 3, 6 and 7 are drawn to methods for detecting a predisposition to a noncryptogenic liver disease comprising analyzing an individual for a change in a genotype of keratin K8 at position 340. The claims include any amino acid change at position 340. While the claims recite that it is a property of a mutation of a CGT to CAT that the mutation is associated with noncryptogenic liver disease, the claims are not limited to methods which detect only the CGT to CAT mutation that encodes codon 340 of the keratin K8 protein. Rather, the claims encompass detecting any amino acid change at position 340, and then only further define the property of a mutation that results from the CGT to CAT mutation. Thereby, as broadly written, the claims encompass detecting a nucleotide alteration resulting in any amino acid change at position 340 of keratin 8 or resulting in a deletion of the amino acid at position 340 of

keratin 8. Claim 4 is considered to be limited to methods wherein the mutation is in the human keratin 8 gene and encodes for the R340H mutation.

While the preamble of the claims recite "an individual human", the claims broadly encompasses analyzing an individual. Accordingly, the claims are considered to include detecting the keratin 8 mutation in any non-human animal, including dogs, goats, horses, monkeys, rats etc. Thus, the claims encompass the detection of a potentially large genus of genotypes that have not been clearly described in terms of any particular structural features.

Additionally, the preamble of claim 1 recites detecting a predisposition to any liver disease. Claims 3, 6 and 7 encompass the detection of a predisposition to any noncryptogenic liver disease. Thus the claims encompass the diagnosis of a predisposition to a wide variety of liver diseases including liver diseases associated with viral hepatitis, alcohol, cystic fibrosis, tumors, polycystic disease, parenteral nutrition-induced, multiple adenomas, and congenital hepatic fibrosis (see, e.g., Table 2 of the specification).

Nature of the Invention

The claims are drawn to methods for detecting a predisposition to a liver disease by assaying for a genotype of a keratin 8 gene. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (page 5) teaches that the keratin 8 nucleic acid sequence was known in the art at the time the invention was made and is provided in GenBank Accession No. NM_002273. The specification further teaches that the keratin 8 nucleic acid sequence is provided as SEQ ID NO: 3 and the amino acid sequence is provided as SEQ ID NO: 4 therein.

The specification teaches the results of a study in which 467 liver explants from patients having liver disease and 349 healthy control blood samples were analyzed for the presence of mutations in the K8 gene. Based on this analysis, the specification identified 14 mutations that were present in the K8 gene – i.e., the mutations encoding for mutations: G52V, Y53H, G61C, R340H, G433S, R453C, I-465(I) RDT (468), I62V, L71L (CTG to CTA), A318S, R201C (CGC to TGC), E376E (GAG to GAA), V460M and V479I (see Table 3). The I62V, A318S, R201C (CGC to TGC), V460M and V479I are described as polymorphisms that are found at similar or higher incidence in controls as compared with individuals having liver disease (see footnote to Table 3). Nine of the mutations are characterized as posing "a potential risk factor for subsequent development of liver cancer" (see footnote for Table 3). However, 3 of these mutations, namely the G52V, R453C and I-465(I) RDT(468) mutations, were found in only a single patient (i.e., 1 out of 467 patients) having liver disease. While the 3 mutations were not found in any of the 349 control blood samples, no results are provided for control liver samples. Given the fact that the 3 mutations were found in only a single patient and that the sample control population was not of an equivalent size as compared to the affected patient population and that no control liver samples were analyzed, the results obtained

from this analysis would not be accepted by those of skill in the art as providing a conclusive correlation between the presence of the mutations and liver disease.

With respect to the elected mutation, the specification teaches that the CGT to CAT mutation encoding for an Arg to His substitution at codon 340 was present in 30/467 (6.4%) human subjects having liver disease and in 10/349 (2.9%) control human subjects (Table 3). The specification further teaches that the K8 R340H mutation was found in human patients having viral hepatitis and in patients with acute fulminant hepatitis (AFH; Table 4). Accordingly, the description has enabled methods of determining whether a human patient has a predisposition to viral hepatitis or AFH by detecting the K8 R340H mutation. However, the specification has not enabled methods for detecting the R340H mutation as indicative of any other liver disease in human or nonhuman subjects. Further, the specification has not enabled detecting a predisposition to a liver disease by detecting a change in any qualitative or quantitative trait of any keratin 8 nucleic acid, such as a change in the quantity of keratin 8 mRNA or DNA.

The Predictability or Unpredictability of the Art :

The art of identifying polymorphisms and determining their association with a disorder, such as liver disease, is highly unpredictable. Knowledge of the sequence of the wildtype keratin 8 gene does not allow one to predict the identity of mutations/polymorphisms in the keratin 8 gene which are correlated with the occurrence of any particular type or all types of liver disease. Polymorphisms are known to occur at a frequency of approximately 1 out of every 1000 bases in the human genome.

However, there is no predictable means for distinguishing between polymorphisms which will be correlated with liver disease and polymorphisms which will not be correlated with the liver disease.

The teachings in the specification support the unpredictability of establishing a correlation between a mutation/polymorphism and the occurrence of liver disease. In particular, the specification (table 3) teaches that while the I62V, A318S, R201C (CGC to TGC), V460M and V479I mutations were present in subjects having liver disease, these mutations were present at a similar or higher incidence in control subjects that do not have liver disease.

Moreover, it is well recognized in the art that the associations between polymorphisms and phenotypic traits are often irreproducible. For example, Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The post-filing date art supports the unpredictability of detecting mutations in the keratin 8 gene as diagnostic of a predisposition to liver disease. For example, Hesse (Journal of Medical Genetics. 2004. 41: e42) analyzed the keratin 8 gene in 256 European Caucasians having diverse liver diseases, but did not detect any amino acid altering mutations in these subjects. A g.740A>G variation was detected in both patients with liver disease and in control subjects. A g.418-4C>G mutation in intron 1 was also detected, but only in one patient with HBV (see page 2, col. 2). Hesse concluded that "(t)he contrary result of our study to the mutations reported so far suggests that allele frequencies might possibly differ between European and North American populations. It might be also possible that additional risk factors coincide with K8 and K18 mutations in Northern American but not European liver patients" (page 3, col. 1).

Similarly, Halangk et al (Journal of Medical Genetics. 2004. 41: e92) studied the prevalence of Y54H and G62C keratin 8 mutations in a population of 1668 patients with liver disease and 679 healthy controls. Halangk did not find an association between the occurrence of these mutations and cryptogenic or noncryptogenic liver disease (page 2, col. 2). The authors indicated that one reason for the discrepancy in the results with those of prior studies may be the fact that their study analyzed subjects having a greater ethnic homogeneity (page 2, final para to page 3, first para).

Additionally, the present claims encompass methods which determine a predisposition to any liver disease by assaying for a R340H mutation. However, the data provided in the specification is limited to the detection of the R340H mutation in subjects having viral hepatitis or AFH. The specification does not teach the frequency

of occurrence of the R340H mutation in other types of liver disease, such as cystic fibrosis or liver tumors. It is highly unpredictable as to whether the results obtained with one type of liver disease can be extrapolated to other types of liver disease.

The teachings in the prior art support the unpredictability of extrapolating the findings of an association between a keratin 8 mutation and one type of liver disease to all other types of liver disease. In particular, by Ku et al (The New England Journal of Medicine, May 2001. 344: 1580-1587; cited in the IDS of November 17, 2005) detected the Gly61Cys and Tyr53His mutations in subjects having cryptogenic cirrhosis, but did not detect these mutations “in the patients with other liver diseases” (see abstract). The "other liver diseases” in which the mutations were not present include hepatitis C, autoimmune hepatitis, acute fulminant hepatitis, primary bilary cirrhosis, Wilson’s disease, hepatitis B and neonatal hepatitis (page 1581, para 1).

Further, the claims encompass determining a predisposition to liver disease in any individual. The specification does not define the term “individual” and thereby the claims include determining a predisposition to liver disease in any non-human animal, such as in a goat, rat, dog, horse, chimpanzee etc. However, the specification does not teach the occurrence of keratin 8 mutations, and particularly the R340H mutation, in a representative number of distinct animals, and an association between keratin 8 mutations or the R340H mutation and various liver diseases. The specification does not disclose a clear structure-function relationship between the claimed mutation and their association with liver disease. There is no showing or evidence which links particular nucleotides in the keratin 8 gene with particular functional properties correlated with

liver disease. The specification (page 27) discusses the potential effects of 4 of the mutations. Namely, the specification suggests that the R340H mutation may be correlated with destabilization, the G433S mutation may be associated with altering keratin phosphorylation, the R453 mutation may be correlated with formation of a disulfide bond and the 1-465(I) RDT (468) mutation may be associated with destablilization. However, the specification does not teach any additional critical sequences or domains in keratin 8 that are required to impart the function of causing or otherwise being associated with any type of cryptogenic or noncryptogenic form of liver disease. The specification (page 28) also teaches that while there are a number of potential functions associated with keratin that may effect liver disease, "the mechanisms by which keratin mutations predispose to cirrhosis remain to be defined." Accordingly, in the absence of a clear structure-function relationship between keratin 8 mutations and the occurrence of liver disease, and in the absence of a representative number of keratin 8 mutations in diverse animals, it is unpredictable if the presence of a qualitative or quantitative change in a keratin 8 genotype can be detected as indicative of liver disease.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The specification does not provide sufficient guidance as to how to detect additional alterations in the keratin K8 gene encoding for a mutation at position 340 of the keratin K8 protein as indicative of any type of cryptogenic or noncryptogenic liver disease. Extensive experimentation would be required to identify additional genotypes

associated with cryptogenic or noncryptogenic liver disease. For example, such experimentation may involve sequencing the keratin 8 gene of individuals having cystic fibrosis to identify mutations, sequencing the keratin 8 gene of individuals that do not have cystic fibrosis, determining the frequency of any mutation present in the individuals having cystic fibrosis and not present in individuals that do not have cystic fibrosis, and performing a statistical analysis to determine whether there is a statistically significant increase or decrease in the occurrence of a mutation in individuals having cystic fibrosis as compared to individuals that have not had cystic fibrosis. Further experimentation may also include performing the above method in a representative number of human subjects having and not having other forms of liver disease, such as hepatitis C, cirrhosis, neonatal hepatitis, liver cancer etc. Additionally, the experimentation may include performing the above methods in a representative number of diverse ethnic populations and in a representative number of distinct animals. Because the outcome of such experimentation cannot be predicted, such experimentation is considered to be undue.

While methods for sequencing nucleic acids are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a particular phenotype. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional mutations in the keratin 8 gene associated with a representative number of diverse types of liver disease.

Working Examples:

The specification provides a working example in which human subjects having viral hepatitis or AFH were genotyped for a mutation in the sequence of the keratin 8 gene encoding codon 340, and the presence of a mutation encoding for a histidine at codon 340 was detected.

However, no working examples are provided wherein the presence of any other alteration at codon 340, including any other amino acid substitution or a deletion of amino acid 340 was detected as indicative of liver disease.

No working examples are provided wherein the R340H mutation is detected as indicative of other types of liver disease, such as neonatal hepatitis or liver cancer.

No working examples are provided wherein any non-human animal subject is determined to have a liver disease by detecting the presence of a nucleic acid encoding the R340X mutation in keratin 8.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v*

Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches an association only between the CGT CAT mutation encoding for an Arg to His substitution at codon 340 of keratin K8 and the occurrence of viral hepatitis or AFH in human subjects, whereas the claims encompass methods for detecting any mutation leading to an alteration at position 340 of keratin K8 as indicative of any type of cryptogenic or noncryptogenic liver disease in a human or non-human subject. The specification does not teach a representative number of keratin 8 mutations that can be used to identify an individual predisposed to any type of liver disease. The specification also does not teach that non-human subjects can be determined to have a predisposition to liver disease by detecting a keratin 8 genotype. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Remarks:

In the response, Applicants traversed this rejection. It is stated that Applicants disclose many mutations in keratin K8 and K18 which are associated with liver. This argument has been fully considered but is not persuasive. With respect to the elected invention, Applicants have established only an association between viral hepatitis and

acute fulminant hepatitis (AFH) and the CGT to CAT mutation encoding for an Arg to His substitution at codon 340 of keratin K8. Applicants have not established that the elected CGT to CAT mutation encoding R340H is associated with a representative number of other noncryptogenic liver diseases or other liver diseases in general.

Applicants point to Table 6 (page 27 of the specification) as teaching the molecular consequences of the keratin mutations. This table indicates that the R340H mutation has the "potential effects" of destabilization. The table does not indicate what is destabilized. Further, while the table lists the potential effect, the table and specification do not in fact establish or provide any type of evidence to show that the mutation in fact has this effect. Most importantly, the specification and response do not explain why this potential effect of destabilization would be expected to cause or otherwise be associated with a representative number of liver diseases or noncryptogenic liver diseases.

Applicants assert that K8 R340H has been shown to be a mutation hot spot. However, the specification and response do not explain why or provide any type of evidence to support an assertion that a mutation hot spot would necessarily be correlated with all types of noncryptogenic liver diseases or other types of liver disease.

The response asserts that the amount of experimentation is routine and the fact that there is some experimentation required does not make the experimentation undue. These arguments have also been fully considered but are not persuasive. It is maintained that the experimentation is undue because the results of such experimentation are highly unpredictable, for the reasons discussed in detail above.

For example, Ku (May 2001) was cited in the above rejection as teaching that while the Gly61Cys and Tyr53His mutations were detected in patients having cryptogenic cirrhosis, these mutations were not detected “in the patients with other liver diseases” (see abstract). The "other liver diseases” in which the mutations were not present include hepatitis C, autoimmune hepatitis, acute fulminant hepatitis, primary bilary cirrhosis, Wilson’s disease, hepatitis B and neonatal hepatitis (page 1581, para 1). The response does not specifically address this reference or this aspect of the rejection.

At page 10 of the response, Applicants state that because working examples have been provided and guidance as to how to test sequences have been provided, “one of skill in the art would be able to perform the experiments as a matter of routine to determine the sequences.” This argument is not convincing because the claims are not directed to methods of determining sequences. Rather, the claims require a known association between any mutation at position 340 of the keratin K8 gene and any noncryptogenic or other type of liver disease in any human or non-human subject. The teachings in the specification and guidance provided in the specification do not enable this broad scope of the claims.

The response states that the invention is not based only on association studies but is also based on animal models. However, the response does not point to any particular teachings in the specification of an animal model that establishes that the R340H mutation or any other mutation at position 340 of the keratin K8 gene is associated with a representative number of distinct kinds of noncryptogenic liver diseases or other liver diseases in a representative number of human and non-human

subjects.

Applicant's response further provides an abstract of the inventors which found that keratin variants predispose to liver failure in multiple ethnic groups. However, it is first noted that the rejection does not limit Applicants to methods for determining a predisposition in particular ethnic groups. Rather, the rejection discusses the findings in the art regarding different ethnic groups in order to establish the high level of unpredictability in the art of identifying mutations in keratin K8 and trying to determine if there is an association between the mutation and liver disease. Secondly, the abstract of the present inventors was not presented in declaratory format. In fact no citation or other evidence is provided to support the statements in the abstract. Thereby, the information in the abstract is not impartial in nature and does not serve as evidence to establish the enablement of the present invention. As stated in MPEP 716.02, "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989).

Note, that this should not be construed as an invitation for providing additional declarations or affidavits. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence

traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

Thirdly, the abstract addresses a R341H mutation, but does not indicate the relationship between the R341H mutation and the presently claimed R340H mutation. Lastly, the abstract does not in fact establish that the R341H mutation discussed therein is associated with liver disease in diverse ethnic populations, as asserted in the response. Rather, the abstract states that the R341H mutation was associated with acute liver failure (ALF)in Caucasians, but does not indicate that the mutation was associated with ALF in other ethnic groups. The abstract actually contradicts Applicants assertion in stating that "some variants segregate with unique ethnic backgrounds."

Applicants point out that claim 3 has been amended so that it is limited to the detection of a specific mutation in keratin K8 in human samples for a predisposition to noncryptogenic liver disease. However, claim 3, as well as claims 1, 6 and 7, are not in fact limited to the analysis of human samples because the claims broadly recite "analyzing an individual." Thereby, the claims are still considered to include the analysis of non-human subjects. Further, claim 3 is not limited to the detection of a specific mutation since claim 3 encompasses the analysis of any genotype of keratin K8 at position 340, and thereby includes detecting any alteration at position 340. Also, claim 3 broadly encompasses predicting a predisposition to any noncryptogenic liver

disease, whereas the specification has established an association only between viral hepatitis and acute fulminant hepatitis (AFH) and the CGT to CAT mutation encoding for an Arg to His substitution at codon 340 of keratin K8.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634